B- Acute Lymphoblastic Leukaemia in A Boy With Xeroderma Pigmentosum

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Abstract

Xeroderma pigmentosum (XP) is an autosomal recessive disorder caused by defect in nucleotide excision repair and is associated with increased incidence of skin cancer. Lymphoblastic leukemia in XP is rare. We report a case of a 11-year-old boy with XP, who developed B – Acute lymphoblastic leukaemia (ALL). He was started on Modified BFM (Berlin-Frankfurt-Münster) ALL Protocol. Tolerance to ALL chemotherapy was good in our XP patient except for the transient derangement of liver function tests during induction, Pseudomonas sepsis and oral mucositis during protocol M and hyperbilirubinemia during maintenance chemotherapy. Though rare, children with XP requires to be investigated for acute leukaemia on development of bicytopenia.

TITLE PAGE

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Abbreviations:

XP	Xeroderma Pigmentosum
B- ALL	B- Acute Lymphoblastic Leukemia
BFM	Berlin-Frankfurt-Münster

XP	Xeroderma Pigmentosum
ALL	Acute Lymphoblastic Leukemia
NER	Nucleotide Excision Repair
UV	Ultraviolet
SCC	Squamous Cell Carcinoma
BCC	Basal Cell Carcinoma
CM	Cutaneous Melanoma
AML	Acute Myeloid Leukemia
AKI	Acute Kidney Injury

Abstract:

Xeroderma pigmentosum (XP) is an autosomal recessive disorder caused by defect in nucleotide excision repair and is associated with increased incidence of skin cancer. Lymphoblastic leukemia in XP is rare. We report a case of a 11-year-old boy with XP, who developed B – Acute lymphoblastic leukaemia (ALL). He was started on Modified BFM (Berlin-Frankfurt-Münster) ALL Protocol. Tolerance to ALL chemotherapy was good in our XP patient except for the transient derangement of liver function tests during induction, Pseudomonas sepsis and oral mucositis during protocol M and hyperbilirubinemia during maintenance chemotherapy. Though rare, children with XP requires to be investigated for acute leukaemia on development of bicytopenia.

Introduction:

Xeroderma pigmentosum (XP) is an autosomal recessive disorder characterised by extreme sensitivity to sunlight, resulting in severe sunburn and pigment changes in the skin. It is caused by defects in genes involved in the repair of ultraviolet induced photoproducts in DNA by nucleotide excision repair (NER). It is associated with greatly elevated incidence of skin cancer.[1,2] It is also associated with malignancies of oral cavity especially squamous cell carcinoma and haematological malignancy especially acute myeloid leukaemia (AML). [3]

Lymphoblastic leukaemia in XP is extremely rare and there are very few case reports of the same[2-4]. We report a case of a 11-year-old boy with XP, who developed B – Acute lymphoblastic leukaemia (B-ALL).

Case report:

An 11-year-old boy, diagnosed to have XP at the age of 6 months, was referred to us with history of fever for 10 days, vomiting and decreased appetite for 5 days. There was no history of bone pains/ bleeding manifestations. Initially he was treated with ayurvedic medications and due to non-improvement, a blood test was done which revealed severe anaemia and thrombocytopenia. Child received packed red cell and platelet transfusions at a nearby tertiary care centre, underwent bone marrow studies, and was referred to our centre with a diagnosis of acute leukaemia for further management.

On physical examination, he had multiple diffuse hyperpigmented macules all over the body with sparing of palms and soles (Figure 1). There was conjunctival congestion with bilateral pterygium (Figure 1) and mild photophobia. There was no pallor, icterus, cyanosis, clubbing, lymphadenopathy or bleeding manifestations. Liver was not enlarged, spleen was palpable 2 cm below right costal margin and testes were normal. The rest of systemic examination was normal.

Blood investigations revealed Haemoglobin: 9.9 gm%, Total leucocyte count: 1100/mm^3, Platelets: 14,000/mm^3. Differential Count: neutrophils 31.3%, Lymphocytes: 66.8%, Eosinophils: 0.2%, Monocytes: 1.2%, Basophils 0.5%. Uric acid: 3.8 mg/dl. Renal and liver function tests were normal. There was no biochemical evidence of tumour lysis syndrome.

Peripheral blood smear showed pancytopenia with 6% immature cells/blasts. Chest X ray was normal. Bone marrow aspiration showed 60% blasts, which were myeloperoxidase negative (Figure 2) and bone marrow flow

cytometry was suggestive of B- Lymphoblastic Leukaemia (CD 5+, CD 10+, CD 19+, CD 20+, cyCD79a+, CD 33 dim positive, CD 34 -, HLA DR +). Cerebro spinal fluid (CSF) study was normal.

Child was treated using Modified BFM (Berlin-Frankfurt-Münster) ALL Protocol. Induction phase included prednisolone, vincristine, daunorubicin, L- Asparaginase and intrathecal methotrexate. He tolerated induction chemotherapy fairly well. He had good prednisolone response on day 8 of steroids with no blasts in the peripheral blood. He had hyperbilirubinemia and transaminitis after day 15 vincristine [S. Bilirubin:1.9 mg/dl (grade 2 CTCAE), SGPT: 248 U/L (grade 2 CTCAE), SGOT: 105 U/L (Grade 1 CTCAE)] during induction chemotherapy, which had improved spontaneously. Hence subsequent Day 22 and Day 29 vincristine were administered at 50 % dose, which he tolerated well without development of further hyperbilirubinemia and transaminitis. Post induction chemotherapy, his bone marrow was in remission. Subsequently, child completed Phase 1B with Cyclophosphamide, 6- Mercaptopurine and Cytosine Arabinoside along with intrathecal methotrexate without any complications. Child subsequently completed interim maintenance with 6- Mercaptopurine and Methotrexate without any toxicities. Child then received protocol M with high dose methotrexate (3 grams/m^2 for cycles 1 and 2 and 5 gram/m^2 for 3 and 4 cycles). He developed grade 2 mucositis after cycle 2. He also developed blood stream infection with Pseudomonas aeruginosa during cycle 3 of protocol M and was treated successfully with Cefoperazone- Sulbactam. Child completed re-intensification phase uneventfully. He is now on maintenance chemotherapy. After six cycles of maintenance, he developed hyperbilirubinemia (S. Bilirubin 2 mg/dL, Grade 2 CTCAE), for which Vincristine dose was reduced by 50%. He did not have any episodes of neutropenia during maintenance.

Discussion:

XP is a rare autosomal recessive disease with 100% penetrance. Patients have sensitivity to ultraviolet (UV) radiation, thereby increasing the risk of cutaneous tumours, such as squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and cutaneous melanoma (CM).[1]The most common cause of death in XP patients is skin cancer[5]

Normal individuals harbouring XPD polymorphisms are at increased risk for developing acute leukaemia. In a study by ElMahgoub IR et.al, which evaluated polymorphisms of xeroderma pigmentosum genes (XPC, XPD, and XPG) and susceptibility to acute leukaemia among a sample of Egyptian patients, homovariant for XPD had four fold increased risk of developing AML (OR = 4.4, P = 0.025) either alone or with variant genotypes of XPC and XPG.[6]

The published cases of XP with haematological malignancies are summarised in table 1. Most of the patients were adolescents, with the youngest being a 7 year old with B-ALL with MDS. Death due to leukaemia and treatment related toxicity were observed in all patients except for one.

Treatment of hematologic malignancies in patients with defective DNA repair pathways requires careful consideration.[8]Patients with XP generally tolerate diagnostic X-rays and radiotherapy.[9] However, sensitivity to certain chemotherapies depends on the specific NER deficiency.[10]

Sumiyoshi et.al[11], reported 2 cases of adults with XP, who were relatives, treated using cisplatin for papillary-predominant adenocarcinoma and squamous cell carcinoma of oesophagus. Both of them had enhanced adverse reactions and antitumor activity. The first patient developed diarrhoea, vomiting, transaminitis, hyperbilirubinemia, acute kidney injury (AKI) requiring haemodialysis and complete hearing loss. The second patient developed hearing impairment requiring hearing aid, AKI and severe myelosuppression, leading to death.

In contrast to these reports, our paediatric patient tolerated induction ALL chemotherapy relatively well. Even though there was transient derangement of liver function tests during induction, Pseudomonas sepsis and oral mucositis during protocol M and hyperbilirubinemia during maintenance, he remains disease free at 26 months from diagnosis.

Conclusion

Though rare, a child with XP requires to be investigated for acute leukaemia on development of bicytopenia. Tolerance to ALL chemotherapy was good in our XP paediatric patient except for the transient derangement of liver function tests, Pseudomonas sepsis and oral mucositis.

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